NPS-OR-94-013

NAVAL POSTGRADUATE SCHOOL

Monterey, California

QUANTITATIVE MODELING AND ANALYSIS IN ENVIRONMENTAL STUDIES

Donald P. Gaver

October 1994

Prepared for:
Naval Postgraduate School
Monterey, CA 93943

NAVAL POSTGRADUATE SCHOOL
MONTEREY, CA 93943-5000

Rear Admiral T. A. Mercer
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This report was prepared for and funded by the Naval Postgraduate School, Monterey, CA.

This report was prepared by:

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1994	Technical

4. TITLE AND SUBTITLE
Quantitative Modeling and Analysis in Environmental Studies

5. FUNDING NUMBERS

6. AUTHOR(S)
Donald P. Gaver

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Naval Postgraduate School
Monterey, CA 93943

8. PERFORMING ORGANIZATION REPORT NUMBER
NPS-OR-94-013

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

This paper reviews some of the many mathematical modeling and statistical data analysis problems that arise in environmental studies. It makes no claim to be comprehensive nor truly up-to-date. It will appear as a chapter in a book on ecotoxicology to be published by CRC Press, probably in 1995. Workshops leading to the book creation were sponsored by The Conte Foundation. The author thanks Dr. Arthur Bloom, Dr. Fred de Serres, and the writing panel for considerable support.

14. SUBJECT TERMS
systems, mathematical models, groundwater models, exposure models, dose-response models, pharmacokinetics, cancer models, pharmacodynamics, model validation, risk assessment

15. NUMBER OF PAGES
58

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

QUANTITATIVE MODELING AND ANALYSIS IN ENVIRONMENTAL STUDIES

Donald P. Gaver
Department of Operations Research
Naval Postgraduate School
Monterey, CA
93943

When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.

William Thompson
Lord Kelvin

"Art is the lie that helps us see the truth," said Picasso, and the same can be said of modelling. On seeing a Picasso sculpture of a goat, we are amazed that his caricature seems more goatlike than the real animal, and we gain a much stronger feeling for "goatness." Similarly, a good mathematical model — though distorted and hence "wrong" like any simplified representation of reality — will reveal some essential components of a complex phenomenon.

Lee A. Segel

The mathematicians are a sort of Frenchmen: when you talk to them, they immediately translate it into their own language, and right away it is something utterly different.

Goethe

Key Words: systems, mathematical models, groundwater models, exposure models, dose-response models, pharmacokinetics, pharmacodynamics cancer models, model validation, risk assessment

1. INTRODUCTION

Most biological systems are complex, being made up of many subtly purposeful, interacting parts. Whenever such complex systems interact with each other or the environment it is useful, or even essential, to introduce a simplified way of thinking about and expressing the possible outcomes. To do so is to employ a *model*. In this chapter we discuss and illustrate some of the types of *mathematical models* that have been developed and found informative by those who study and attempt to control biological and physical environmental systems. In particular, we examine mathematical models for the interaction, eventual disposition or fate, and effect, of biological and chemical agents that have been released into the physical environment by mankind, have dispersed and accumulated, are potentially harmful to the natural environment, including mankind, and hence are candidates for remediation.

Biological scientists are more accustomed to work with and think in terms of physical biological models, *e.g.* laboratory animals, than with the quantitative mathematical models that are our topic. However, the use of mathematical models in biology has a long and honorable history: early examples include population growth models by Volterra and Lotka, and the genetic models of Mendel, Fisher and others. An excellent single reference is the book of Murray (1980). Statistical models that represent individual physical variations, such as in height, weight, blood pressure and pulse rate and many other physiological characteristics, are in routine use, as are models that describe human response to doses of drugs, medicines, or exposure to toxic agents in various forms and concentrations. These latter will be reviewed in this chapter.

Environmental problems encountered by mankind typically involve control of the production and emission, dispersion, interactions, location, fates, and effects of numerous biological, chemical, and physical (such as ionizing radiation) components within the environment. Understanding and control of the many interrelated processes involved is well beyond the scope of simple field experimentation alone, just as it transcends the boundaries of the single traditional scientific disciplines and technologies. An overall logical framework is needed to assemble the various system components so that options can be expeditiously compared on the bases of costs and effectiveness. Mathematical, often computer-activated, models are a useful, and increasingly utilized, tool for economically exploring the cost and effectiveness of different options for environmental usage and control. This exploration makes use of scientific information and available data pertinent to the particular situations of concern, for example at those sites that are candidates for remediation. In addition, modeling efforts now guide the collection of suitable meaningful data, and help to organize and focus their summary and analysis. Such focusing is accomplished by initially combining data and theoretical understanding from the various relevant scientific disciplines and technologies in an attempt to address meaningful questions that are generally, if simplistically, of the form "If option X is used for remediating hazardous waste site Y, what will be the cost, how long will be required, and what will be the change in the habitability, or risk, associated with the site?" It is increasingly recognized that there is considerable uncertainty attached to quantitative responses of the types described. Thorough and careful appraisal

and communication of that uncertainty to policy makers and the public is the responsibility of the growing fields of *risk analysis* and *risk communication*.

This chapter considers several of the generic modeling areas encountered in environmental studies. No attempt is made to be detailed or encyclopedic. We attempt to present the flavor of the area and to put the reader into contact with relevant literature and references thereto. The aim is to provide an overview of models for certain of the many major components of a *risk characterization* analysis or study.

A graphical flow chart or *influence diagram* appears as Figure 1.

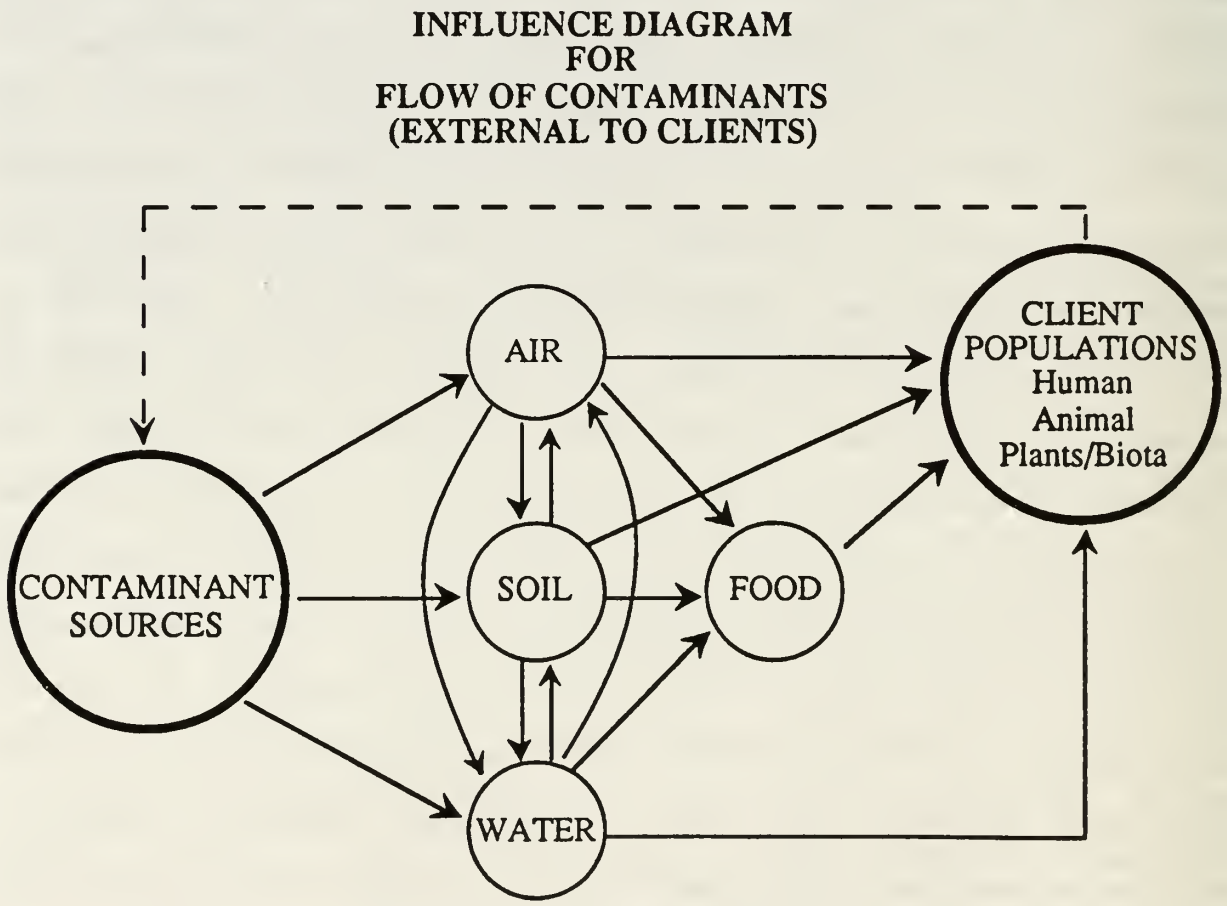

Figure 1

The links between the round nodes show the direction of influence of contaminants that enter the environmental system and are transported to such client populations as humans, animals, and plants. We use a dotted arrow to denote the influence of client populations, such as humans, upon the contaminant sources. Needless to say, models for the behavior of all sources and links will not be exhaustively discussed in this chapter.

Section 2 outlines modeling issues connected with *groundwater*, a vital resource, and also a primary medium of transport of pollutants. The history of models in this area is long, and the subject is highly technical, requiring the intellectual tools of physics and engineering, applied mathematics, numerical analysis and statistics, as well as chemistry and biology. Groundwater is one of the many media by which human beings, plants and animals come into contact with chemical and biological pollutants and toxicants. Maintenance of its quality is a matter of primary concern to the United States Environmental Protection Agency.

In Section 3 we consider *compartmental* and *physiologically-based pharmacokinetic models* for the description of the transport patterns of concentration of toxic agents, and also medicines, between and within bodily organs. Thus, given exposure to various chemicals *via* drinking, cooking and washing water (but also through air, food, *etc.*) it is natural to ask about their ultimate concentrations in the blood that enters such organs as the liver or kidney. Pharmacokinetic models describe the time-dependent relationship of that concentration, or dosage, in terms of exposure routes to the host organism, *e.g.* a human being, and the scheme by which blood flows, and its contents modified, in that organism on the way to target organs.

Intake from groundwater provides one of the many exposure routes referred to above.

Section 4 provides an introductory account of the active new field of *exposure monitoring and modeling*. Reflection suggests that careful effort is needed to relate the origin and subsequent transport of pollutants, *e.g.* through groundwater, to the exposure and dosage of humans and other endpoints, such as the DNA adducts discussed in another chapter.

The topic of Section 5 is that of *dose-response models*. Such models connect dosage levels, *i.e.* concentrations of toxic chemicals or biological agents, to response at the organ, or host organism, level; response may be in terms such as illness or death of the organism or modification of an organ, *i.e.* the proliferation of cells or the conversion of healthy cells to precancerous or cancerous. Such events are called *endpoints;* current attention appears to be focused on increasingly more biologically basic, and subtle, endpoints. The mathematical models that have been proposed reflect biological phenomena to as great a degree as possible, but that degree is limited in practice by the complexity and imperfect knowledge of the variety of biological processes by which alien substances actually alter organs. Figure 2 describes the interactions envisioned, and modeled, in the categories alluded to above.

Section 6 discusses some of the issues associated with model-based *risk assessment*. The challenge is to represent multi-stage organ alteration processes credibly by models that are simple enough to be estimated from available and relevant data. Major interest focuses on the effects of chemical

INFLUENCE DIAGRAM
FOR
FLOW OF CONTAMINANTS
(INTERNAL TO HUMAN AND ANIMAL CLIENTS)

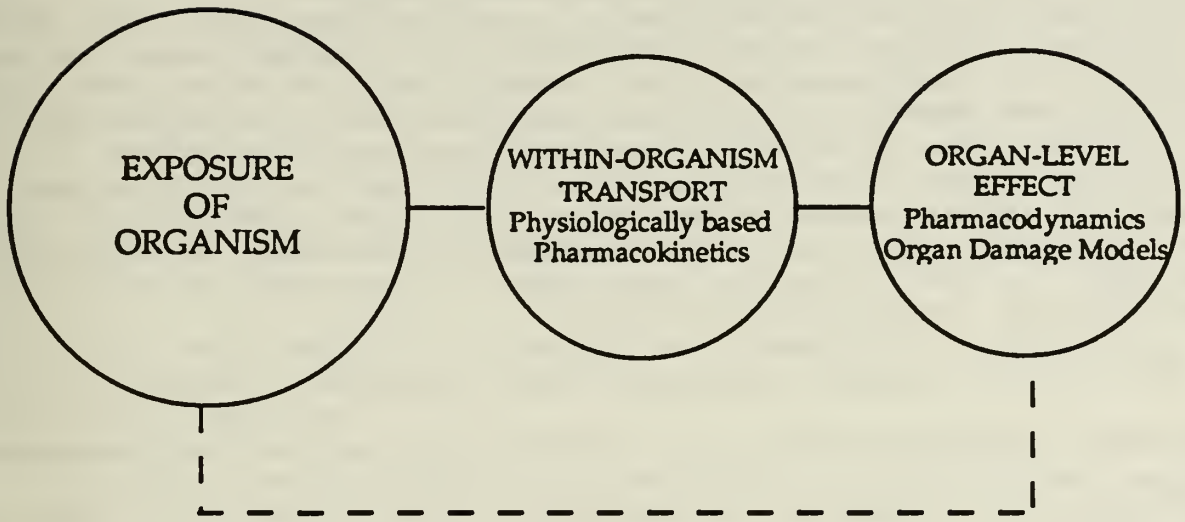

Figure 2

or biological agents on human beings. Often dosages of such agents are low, but prolonged, although response to sudden impulse dosage can be of concern, *e.g.* that caused by accidental spill. Direct experimental human response information is seldom available, so indication of effect is often sought in animal experimentation; *animal* includes rodents, but also fish, frog embryo, and many other *biological models*. For reasons of economy and time such experimentation are often done at relatively high doses. It is current practice to extrapolate such animal data to indicate the animal responses at low doses, and across species to a corresponding response in man. The extrapolations are typically made in terms of mathematical models. Such assessments are uncertain and vulnerable for various reasons, and the results have been questioned. The techniques that have been proposed to circumvent the criticisms seem currently to be two-fold: to increase the size of the animal

experiments, thus allowing more confident determination of low-dose effects, and to improve upon the biological credibility of the basic models. However, very large animal studies are costly, and hence rare. References are given later to the current discussion on extrapolation problems.

Section 7 outlines, in two epidemiologic case studies, issues that were confronted when quantitative approaches, including the use of mathematical and statistical models, were employed to analyze risk to humans exposed to chemically polluted drinking water. Techniques are discussed, as are problems associated with interpretation of results.

The various sections described above ultimately pertain to *risk assessment, characterization, and analysis*. The task of risk assessment, characterization, analysis, and management, is to estimate the effect on environmental clients, e.*g.* humankind but not exclusively so, of admission of certain chemicals and biological agents into the environmental system. Such admission may be appealing in many ways, for instance economically, but the appeal must be balanced against possible adverse effects. Risk analysis attempts to quantify such effects in an atmosphere of considerable uncertainty. In each of the sections above we point to efforts made to quantify the uncertainties inherent in the modeling efforts and their applications. Numerous references are presented to supplement the discussion. There remains much to be done to reduce and characterize such uncertainty.

2. MODELING GROUNDWATER: A SPECIFIC SYSTEM RELEVANT TO REMEDIATION ISSUES

Water is essential for sustaining life on Earth. It is also the medium that transports many of the pollutants that are introduced into the natural environment. *Groundwater*, which is the earth surface's source of most of the

water that humans come into contact with, is an element of the *hydrosphere*, which itself acts as a system. The latter encompasses all waters above, on, and below the surface of the earth. Water moves cyclically through this closed system, being exchanged from state to state by evaporation, precipitation, plant transpiration and other processes including human usage and consumption: *i.e.* it enters the groundwater subsystem in recharge zones and leaves in discharge areas. While doing so it is consumed by humans, plants, and animals, contributes to disposing of their waste products, and is faced with increasingly many demands as a medium for disposing of agricultural and technological byproducts.

Groundwater modeling refers to the description, in quantitative numerical terms, of the flow, and residence or storage, of water into, and out of, regions near the surface of the earth. Although such flow is of natural origin it is affected by man's activities such as pumping out of and into those regions. See van der Heijde *et al.* (1988), Schwartz *et al.* (1990), Anderson and Woessner (1992), and numerous articles in the journal *Water Resources Research* and elsewhere. The objectives of modeling are both to build a scientific basis for understanding the many interacting processes involved and to provide specific information for managing an essential, scarce, resource. Public concern is with the adequate supply of water for human consumption and usage, and increasingly with the quality of that supply. Models help to inform policy makers of the effects of regulations placed on water usage for direct human consumption and waste disposal, and also on the impacts of usage for waste disposal by the agricultural, manufacturing, electric power,

transportation and defense subsystems of the economy. They provide information concerning the status and cost-effectiveness of remediation efforts.

Models for such purposes use geological, chemical and biological science and principles of fluid mechanics to describe the time and spatially varying and interacting flows of relevant fluids: fresh water in aquifer containment, but also, where relevant, the extent of intruding salt water, petroleum, and solutions of chemicals such as fertilizers and pesticides, radionuclides, and other items. Specialized multicomponent models are used to assess, the chemical-biological content of groundwater: important classes are *solute transport models* and *pollutant transformation and degradation models*. In these, the processes of change of transported or resident pollutants are described and predicted, using appropriate chemical and biological science. An important objective is to track the availability for consumption by mankind of various substances that enter the water cycle at various remote points and reach aquifers that yield drinking water.

Since groundwater carries contaminants, its motion is of primary importance. That motion is best understood and mathematically modeled in fully saturated regions inhabited by porous materials such as rock or soil. Aquifers are such regions: they store water accessed by wells that furnish water for consumption. Widely accepted mathematical models for aquifer flow are based on physical conservation laws that govern fluid flow; these models are called the Navier-Stokes equations. For use in the porous media groundwater environment these in turn may be simplified by use of the semi-empirical Darcy law; see Schwartz *et al.* (1990), Chapter 3, for a discussion of the extent of this law's applicability. The result is a linear second-order partial differential

equation for *pressure head* that involves a hydraulic conductivity "parameter" (actually a function of space as that reflects regional variation), a storage term, and a source-sink term. The latter represents natural flow into and out of the aquifer via, say, rainfall, plus the influence of pumping for direct usage plus recycling remediation, *i.e.* the recharge and discharge areas previously mentioned. This setup is called the *porous media* model. Given these data requirements, plus boundary and initial conditions, partial differential equations can be solved numerically to describe pressure head as a function of space and time throughout the aquifer. From head information, flow velocities can be derived, and these allow prediction of the concentration of a dissolved chemical solute at a specified place and time in an aquifer, since the chemical solution is regarded as being largely transported by the process of *advection*, *i.e.* flow along with the general groundwater. In addition, the solute *disperses;* the dispersion flux is sometimes viewed as depending on the current concentration gradient (Fick's law). Further models are needed, and to some extent available, for describing chemical reactions, abiotic transformation, and biological processes between many possible inorganic and organic solute types; see Schwartz *et al.* (1990), Chapter 4. Basic spatial and temporal change in solute concentration is also modeled by second-order partial differential equations, coefficients of which depend on the flow rates, obtained as sketched earlier, and on local dispersivities.

Despite the availability of the fundamental fluid-mechanical science on which modeling of flows in saturated media can be based, various approximations are required in practice. Hydraulic conductivity "parameters" may not be conveniently nearly constant, much less well-known, over the entire

region of interest, so that in practice regions are divided into *hydrostratigraphic* units (regions of similar hydrogeological properties) within each of which nearly the same parameter values are assumed to prevail; see Anderson and Woessner (1992), Chapter 3, for practical details. It has been noted that good prediction of dispersive effects depends on accurate calculation of the spatially varying velocity field to a high degree of resolution, which is difficult because of lack of information concerning influential local variations in hydraulic conductivity. It is thus difficult to make highly accurate predictions of contaminant concentration at various locations in an aquifer, *e.g.* near a well location.

Contaminants typically enter the saturated regions addressed earlier through unsaturated zones, *e.g.* through soil, possibly from near-surface disposal, or spills, of contaminants. The type of liquid saturation in these zones is water or non-aqueous-phase liquids, plus gases. Although Darcy's law remains approximately applicable in unsaturated flow the hydraulic conductivity parameter, K, is now a function of the head, so the partial differential equation becomes non-linear, increasing difficulties with numerical solutions. Several approximate analytical forms have been proposed to describe $K = K(h)$; see Schwartz *et al.* (1990), Chapter 3. Furthermore, unsteady and transient flows in the unsaturated zones are the rule, whereas the flow in saturated regions tends to be steady. These features further complicate model parameter specification and equation solution. Transport of contaminants in unsaturated regions also is subject to a greater number of physical and biological processes that are interactive, complex, and less well-understood than are those in the saturated regions.

Still more serious complications arise when modeling the flow of water and dissolved contaminants through rocky media that is extensively fractured. Such fractures form haphazardly placed channels with apertures of varying sizes, and hence flow capacities. The hydraulic conductivities of fractured media may actually change with applied stress, so that pumping from a well in such regions can alter the effective porosity of the region changing its flows. Various modeling options have been employed to handle the fractured-media flow problem. A first approach is to make a continuum approximation: one represents fractured media flow as that in an equivalent porous media, defining a hydraulic conductivity parameter to be incorporated into the aforementioned partial differential equation; this is now called an equivalent porous media model. This approach is inaccurate if the region is connected but very sparsely fractured; *i.e.* if a small local region is being considered. A second approach assumes dual porosity, meaning that the porosities of the rock matrix and of the fractures are separately identified, as are flows within and between rock and fractures; the model is now two coupled partial differential equations and is referred to as a dual porous media model. Finally, if fracture flow predominates (rock is relatively impermeable), the flow is modeled as occurring through a network; this is the discrete fracture model. Practical uncertainties exist as to an actual fracture configuration, which add to the uncertainty of prediction of flows or water plus transported pollutants.

Various methods of ascertaining properties of underground regions are in use so that roughly appropriate choices of flow and transport models can be made. These include evidence from bore holes, the application of *kriging*

(interpolation between spatially separated observations, see Cressie (1991)), use of tracer information, inverse problem solution (inference of concealed hydraulic parameters from head and flow observation), and others; see Anderson and Woessner (1992), Chapter 8, on the *calibration process*, wherein a model is adjusted to fit available data and the success of the fit is examined.

Uncertainty, Variability and Stochastic Models

Sizable heterogeneity and irregularity of media through which water — and contaminants — pass and are stored has prompted the development of *probabilistic* or *stochastic* (=chance=random) models to supplement the earlier deterministic versions. For example, Gelhar (1986) treats the logarithm of the hydraulic conductivity, K, as a spatially correlated Gaussian random process, which he then uses to characterize the induced head statistics, *e.g.* its variance. He utilizes mathematical techniques to deduce that "the large-scale transmissivity (hydraulic conductivity) of an aquifer is obtained by averaging the logarithms of local transmissivities that are measured." It is stated that the same approach can be used to evaluate an effective large-scale dispersion coefficient (the "macrodispersivity") relevant to solute transport. More recent work by Glimm and Sharp (1991), and by Zhang (1992), expand upon the characterizations of heterogeneous porous media — the habitat of groundwater — as general random fields. The assumption of the log-Gaussian (or log normal) distribution for hydraulic conductivity goes back at least to Freeze (1975). It is legitimate to ask about the sensitivity of results based on this approach to its assumptions, *i.e.* that of Gaussian distributions, for in other areas there occur extensively tail-dispersed and otherwise non-Gaussian distributions.

Note that randomness may enter the groundwater picture not only by way of media characterization, as above, but through representation of the recharge process, which is influenced by the irregular occurrence of rain, snow, and heat. Chemical and biological processes occurring in the subsurface environment are also so affected. In summary, significant fluctuation and variability (sometimes called *structural randomness*) may well occur in media, recharge and discharge, and in the properties of the items transported therein. Early models ignored such effects: more modern models include such realisms.

An additional component of uncertainty or randomness results from errors inherent in the measurement process for determining properties of the media and inputs and outputs at particular sites from observations; this component may be called *measurement error* or *statistical randomness*. In the literature, see Anderson and Woessner (1992), measurement errors are also frequently characterized by a Gaussian or normal distribution: the familiar "bell-shaped curve." However, an extensive statistical literature on robustness suggests caution; see Tukey (1984), p. 614. In particular, care should be taken in the application of ordinary least-squares regression techniques: these tend to be undesirably responsive to isolated outlying observations. Such comments potentially apply to kriging, a technique for smoothing and interpolating noisy spatial observations that is increasingly applied in groundwater studies. Cressie (1991) considers *robust kriging*, a technique that down-weights isolated maverick observations that are the result of aberrant measurements.

Since both structural randomness and random measurement errors seen plausible and have been invoked, their blending in a *Bayesian approach* suggests itself, see Berger (1985). Such an approach is briefly mentioned by Anderson and Woessner (1992) who refer to work by Freeze *et al.* (1990). Briefly, Bayesian theory (named for the Reverend Thomas Bayes, 1763), see Berger (1985), represents uncertainty in a physical or biological parameter by calculating its probability distribution, the so-called *posterior distribution*. The components of this distribution are a *prior distribution*, which incorporates general information about the unknown value obtained from other situations and expert judgment, as well as a likelihood function that represents the information given by measurements on the specific situation of concern. For the mechanics, see Berger (1985). The Bayesian methodology is capable of formally incorporating information from other, similar, sites into the estimation of properties of a site of current concern, as well as measurements taken at the latter. The classical statistical approach omits formal treatment of information other than that obtained at a particular site. There apparently exist computer codes for carrying out such processes; several references are given by Anderson and Woessner (1992), Chapter 8. A Bayes version of kriging exists; for an account again see Cressie (1991).

Another approach to the uncertainty problems in the groundwater arena is that of *expert systems*, or more generally *artificial intelligence* (AI). Several publications and expert system tools such as knowledge bases and inference engines are referenced in Schwartz *et al.* (1990), Chapter 7. For a way into AI and uncertainty ideas, see Pearl (1988).

Remediation of contaminant content of groundwater is often attempted by pumping fresh (low or uncontaminated) water into and out of aquifers in an attempt to dilute and flush out existing contamination. The effectiveness of this methodology depends upon the nature of the contaminant; if the contaminants are multiphasic non-soluble (immiscible) and have been trapped in pores of rocks or soils their removal by pumping technology is extremely slow; see Travis (1992).

3. COMPARTMENT AND PHARMACOKINETIC MODELS

Models that envision either the physical environment or an animal or human body as a collection of inter-linked but homogeneous *compartments* are called *compartment* or *pharmacokinetic models*. They behave as follows: a substance enters one or more compartments according to a specified time pattern; once in the compartment it resides there for a characteristic time before it changes form, disappears, or passes to another compartment, where the process continues; cycling back and forth between compartments may occur. The substance may in fact be a combination of more elementary substances. The agent that carries the specified substance can be blood or other bodily fluids, so the amount present is naturally expressed as a concentration. In the case of animal or human body compartments, the modeler's goal may be to predict the dosage and transformation of a medicine, drug, anesthesia, or possibly toxin, at a particular organ, such as the liver. The varying rate at which dosage is eventually administered to the target organ depends upon the rate of substance entry into the blood stream, *e.g.* from the lung or stomach, and thereafter on the rate of transfer within and between organs that precede the target organ in natural order, and also on the blood flow rate. The term

pharmacokinetics is used to describe this process when the context is generally biological. Classical pharmacokinetic models are expressed in terms of systems of linear ordinary differential equations with constant coefficients that reflect the rate at which concentration changes in the various compartments. Physiologically-based pharmacokinetic models (PB,PK for short) utilize physiological/biological interpretations of mechanism to specify the equation coefficients, which may not be constant in concentration, and may In fact be non-constant. PB,PK models are, theoretically, capable of validly representing intraspecies biological responses, and to give promise of useful interspecies extrapolations. See Bischoff (1987) for more details. Quite recent work by Bois, Gelman, Jiang and Maszle (1994) has applied modern Bayesian statistics to fit a pharmacokinetic-physiological toxicokinetic model to assess fraction of tetracholoroethylene metabolized at a given dose level, taking account of individual variability plus estimation uncertainty.

Analogous models can be used to describe the flow or transfer of dissolved chemicals, pesticides or waste material from the earth's surface through soil and rock to groundwater in aquifers. Presumably the predicted concentrations of such items in, say drinking or washing water, which may be understood as the output of an appropriate *environmental component (compartment) model*, provide inputs to a *pharmacokinetic (compartment) model* eventually describing the dosage of (some transformation of) the dissolved and transported chemical to a particular target organ within a human body or another organism. This dosage could, in turn, provide input to a *pharmacodynamic model*, *e.g.* a multi-hit or clonal expansion model, *cf.* Moolgavkar and Luebeck (1990), or Portier (1989) to predict the occurrence of

carcinogenetic material in an animal or human organism. A nice overview of PB,PK compartment models is given by Andersen (1987). A list of open problems awaiting solution to provide improved risk analysis tools is in Rhomberg (1988). More detail and further references occur in Section 5, on dose-response models.

PB,PK models have been tested empirically by several groups of investigators. For example, see Andersen, Clewell, Gargas, Smith, and Reitz (1987), Reitz, Nolan, and Schumann (1987), who studied methylene chloride, and Travis, Quillen, and Arms (1990) who examined benzene. In both of these latter cases data from rats, mice and humans were modeled with the objective of explaining or relating concentrations of items in question (methylene chloride and benzene respectively) and their metabolites in target organs. These studies have as an objective the reconciliation of various empirical investigations on the basis of plausible biological mechanism.

The strategy currently followed in applications of PB,PK thinking is, first, to identify physiologically meaningful compartments; in the methylene chloride case four were used: liver (the primary metabolizer), fat, organs such as brain, heart, kidney, other viscera, and muscle; in the benzene case bone marrow was added, for it and liver are the primary organs that metabolize benzene. The differential equation coefficient values are then specified from previous related experimental studies. Explicit recognition is given to nonlinear process-saturation terms such as the Michaelis-Menton expression used in modeling metabolism and also to gastric absorption rate as a function of dose level. In Travis *et al.* (1990) the Michaelis-Menton parameters, V_{max} and K_m were actually determined by fitting the model to existing data. After

the model is fully specified it is asked to explain data on concentrations of the dosed material or its metabolites at target organs. In both Reitz *et al.* (1987) and Travis *et al.* (1990) objectives are predictions of responses, *i.e.* concentration in an important organ, or other endpoints, as a function of time. In general, agreement appears qualitatively reasonable to good. However, some such published comparisons appear to depend on parameter values obtained from the data being described, so the term "prediction" is perhaps a bit generous. To test true predictive capability of a model it would be necessary to apply it to an independent data set: apparently this has been done in some cases with reasonable success.

A good modern introduction to pharmacokinetic modeling is Gillette and Jollow (1987). There the reader will find several references to validation of models; although details are not given they can presumably be obtained from the authors.

Uncertainty, Variability and Stochastic Models

It is clear that the response of even quite similar organisms to controlled doses of a medicine or possible toxin will vary somewhat inexplicably, suggesting the need for models that enhance the original, deterministic, ordinary-differential-equation setups. An initial step has been to provide or adapt models to express concentrations as randomly varying around a mean. Thus the models represent the *number* of elementary particles of a foreign element, *e.g.* a chemical, in a compartment as fluctuating randomly, and often independently, governed by fixed (and known) transition probabilities. This phenomenon can be called *outcome variability*. Later approaches capitalized on the large numbers (or particles) involved by using

continuous (diffusion) approximations, *cf.* Lehoczky and Gaver (1977). The latter approach has the advantage of close contact with the initial deterministic models (the latter gives precisely the mean of the later diffusion approximation) and of furnishing a description of random fluctuation around that mean that is the familiar Gaussian. However, the scale of random fluctuation is on the order of the square root of the mean, which may be smaller than that observed in practice. Outcome variability can be negligible in practice.

A second, and possibly dominant, source of variability is in the parameters of the differential equation themselves: it is plausible that these vary in time within individual organisms, and, possibly more importantly, between organisms. This variability is entirely analogous to the structural variability mentioned in connection to groundwater in models in Section 2. Various researchers have incorporated the between-organism component into analyses: Sheiner and Beal (1980) have provided NONMEM (nonlinear Mixed Effects Model) which computes an approximate joint Bayesian posterior distribution of the various parameters in a given compartment model (this is treated as log-multivariate Gauss/normal) and thence to compute the (posterior-based) estimate of, say, a concentration at a target organ; PREDPP is a package used by NONMEM for this purpose. The latter calculation is accomplished either by Monte Carlo simulation ("bootstrapping") from the above parameter posterior or by an approximate numerical calculation. Other investigators, *e.g.* Farrar, *et al.* (1989), have taken the bootstrapping route as well. A further step, taken by some investigators, is to invoke Bayesian formalism to infer, predict, and *control* (in the case of a drug or anesthesia)

the concentration of a substance at a target organ in a particular individual, in the face of uncertainty as to how that individual is processing the substance input, and allowing for measurement error; see Bois *et al.* (1994).

The above approaches all treat model coefficients as constants that are picked from a population described by a distribution but thereafter held fixed. To date it appears that little successful work has been done to characterize the effect of random temporal parameter variability on target concentration variation in an individual organ, although such a model might well be more realistic than those discussed. Models exist in which parameters change because of the presence of pharmaceuticals or toxins; see Jackson (1993) and Gaver, Jacobs, and Carpenter (1994).

Although a considerable amount of effort has been devoted to modeling uncertainty in pharmacokinetic compartment model parameters, very few of the results seem to have been adapted for the use of compartment modelers in the environmental sciences. See MacKay and Peterson (1991) who are concerned with modeling the environmental fate of organic chemicals (pesticides, PCBs, wood preservatives, incineration byproducts, *etc.*) that, purposefully or inadvertently, enter the environment and proceed through soil, water and air to expose humans, plants and animals. The effect of uncertainties in the various parameters (transport and partition) can be addressed by the resampling or bootstrapping approach of Efron and Tibshirani (1986), assuming existence of information concerning their distribution. The same is true in compartment-model studies of persistent contaminants that concentrate in food chains; see Moriarty (1984), who fits a three-compartment model for dieldrin

absorption in tissue; stochastic models are mentioned in passing but are not actually applied.

4. HUMAN EXPOSURE MODELING AND ANALYSIS

Environmental regulation is intended to protect human public health and welfare from adverse effects of environmental pollution. Environmental remediation involves reduction of environmental pollution levels to or below some tolerable level, and the maintenance of that condition. Thus formal regulatory demands and common sense suggest that the level of pollutant to which actual human beings are exposed when in a neighborhood of one or more polluting sources is of direct relevance. Consequences of experiencing various levels of different pollutants via various exposure routes (air, water, food, soil) must often be assessed by models: candidates are physiologically-based pharmacokinetic models that predict the within-organism transfer of polluting chemicals by way of intake from external sources to organs; thereafter one or more *dose-response*, or *pharmacodynamic* models (see next section) are invoked to convert organ-level dosage to biological responses or endpoints such as the occurrence of carcinogenic material or other disease forms.

The importance of quantifying the link between the presence of pollutants in a medium and resulting human exposure has stimulated the development and use of a number of computer models. In 1987 the Environmental Protection Agency established the Center for Exposure Assessment Modeling (CEAM) in Athens, Georgia. According to Ambrose and Barnwell (1989), that office supplies "predictive exposure assessment techniques for aquatic, atmospheric, terrestrial, and multimedia pathways for organic chemicals and metals"; the techniques are in the form of computer modeling packages that are made

available to users on diskettes. A general description of a number of the available models is contained in Ambrose and Barnwell (1989). Such models are generally descriptive of pollutant concentrations in the physical environment but do not appear to make a quantitative connection between such concentrations and the actual uptake of such pollutants by humans, or other inhabitants of the surrounding ecological system.

Efforts to quantitatively monitor individual human exposure to pollutants, *e.g.* within particular closed spaces or near hazardous sites, are described by Ott (1990). The approach has been called Total Human Exposure (THE). Briefly, there are two versions of THE. In the *direct approach* a probability sample of individuals is selected that is representative of a particular exposed population. With the aid of personal exposure meters carried by those sampled, supplemented by their activity diaries, the attempt is made to relate individual exposure to sources of pollution in a great many media. In addition, the body burden of various pollutants is measured. The results from the probability sample can be applied to make statistical inferences concerning population exposure or dose. The latter data can be used as input to dose-response models, see Section 5 to follow, so as to infer that population's risk. The direct exposure monitoring approach has been called the Total Exposure Assessment Methodology (TEAM); apparently a number of TEAM field studies have been conducted in various cities. Among the reported findings is that the number of indoor sources of toxic agents exceeds the number of outdoor sources; the dosage levels indoors can also be much higher than those outdoors owing to exposure to cleaning fluids, paints and CO_2 in enclosed conditions such as homes and offices.

The *indirect approach* to exposure assessment is more truly *exposure modeling*. Field data serve as input to characterize pollutant concentrations in various microenvironments (locations of homogeneous pollutant concentration) and the randomly varying times spent in these by individuals; see Duan (1991). Such models can possibly be used to augment direct exposure assessments to predict human exposure under changed conditions. For more references and details see Ott (1990).

5. DOSE-RESPONSE MODELS

Suppose a dose of a single, or specified combination, of chemicals is imbibed by a human subject, or a wild or laboratory animal. It is of interest to relate the *response* of such subjects to the type and level or concentration of the dose received. This activity is called dose-response modeling, and is an important part of a quantitative risk assessment.

It is usual to assess individual response in binary terms: either a subject has reached some specified endpoint, *e.g.* exhibited tumors of a certain type in a target organ at time of observation (in animal cases, sacrifice), or it has not. Less frequently, more complicated responses are considered; *e.g.* Zhu, Krewski and Ross (1992), in a developmental toxicology context, record and analyze multiple responses of female rats and mice (and their offspring) exposed to the toxin, 2,4,5-T. We concentrate here on binary responses, although information may well be lost in some cases by doing so.

If individuals subjected to a specified dosage level are representative of a given population some will, and the remainder will not, exhibit a positive response. It is useful to think of the fraction that do respond as an estimate of the *probability* that a random number of the population will

respond. The relationship between dosage level or concentration, d, and the probability of a particular response as a function of d, *i.e.* $P(d)$ will typically appear as shown below in Figure 3:

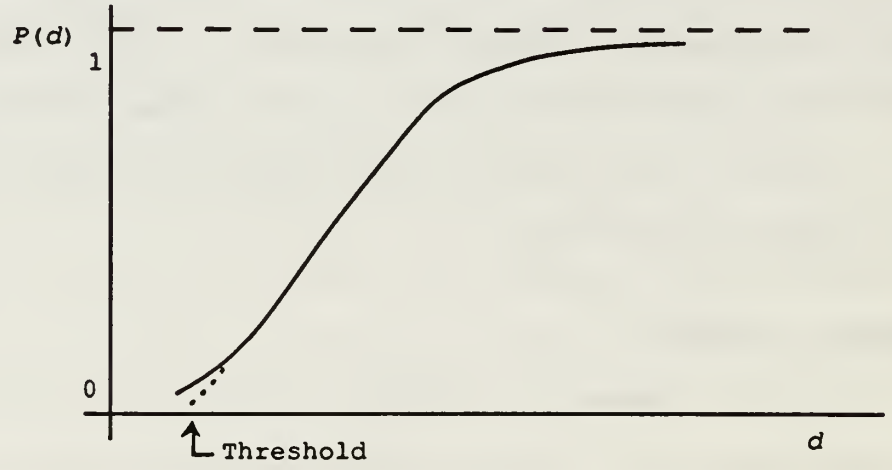

Figure 3

One anticipates that the probability of a positive response, such as exhibition of one or more tumors in the liver after sacrifice, will be monotonically increasing as depicted, at least in large enough samples so that random fluctuations are small. However, reversals do occur and may have biological significance, *i.e.* are not individual sampling variations.

Mathematical representations of dose-response relationships are of two general types. The *simple statistical* type selects a standard statistical model such as the Gaussian/normal "bell-shaped curve", or, alternatively, the so-called Weibull distribution first introduced as a descriptor of mechanical system failure time, and converts that model into a dose-response model. A good introduction to such setups is provided by Kalbfleisch and Prentice (1980), who also discuss the fitting of such models to data, accounting for complications that occur when data are missing (test animals have died before

the planned time of sacrifice), and additional data are available to adjust for differences in individual age, gender, or environmental conditions such as temperature. A particularly effective and popular model of this latter type is the so-called *Cox regression model;* see Cox (1972, 1984).

A conceptually appealing alternative and supplement to the simple statistical models are called *pharmacodynamic models;* these attempt to mathematically represent some of the detailed biological mechanisms that influence organ response. Excellent examples are the *multistage cell-proliferation clonal expansion* models described by Moolgavkar and Venzon (1979), Moolgavkar and Luebeck (1991), and Kopp-Schneider, Portier and Rippman (1991). The importance of cell proliferation in the cancer-development process has been noted early; a modern account is by Cohen, Portier, and Ellwein (1991), and a deterministic dynamic simulation model has been presented by Ellwein and Cohen (1992). There are many papers in this general area. See also Hart *et al.* 1986, p. 217. All of the above models explicitly consider the following multistage process that is currently thought to lead to cancerous tumors: first, an *initiator event* occurs randomly at single-cell level and causes permanent genetic damage. After such an event, cell division yields an increasing number of precancerous clones. The clones so generated may independently die and replicate. *Promoter events,* usually considered to be a second gene-damaging event, may lead to the initiated cells becoming a cancerous lesion or tumor, a typical dose-response endpoint.

The above types of models have been converted to dose-response models by various authors. The procedure has generally been to express initiation, proliferation and completion rates as linear functions of dosages, somehow

expressed (any, but often non-decreasing *positive*, function of time-dependent concentration is presumably minimally acceptable); see Crump and Howe (1984), Murdoch and Krewski (1988), Kodell, Krewski, and Zielinski (1991) for example. All of these approaches resemble each other in that they *postulate* a simple mathematical relationship between dose or exposure and biologically-based model parameters such as the aforementioned rates. While the above step is natural it seems possible that models that more faithfully reflect the actual mechanistic interactions between potential toxic agents and cells at a molecular level could have increased credibility over wider ranges of dosage. In particular, the low-dose and across-species response is of interest in risk assessment; see below; see Portier (1989), especially pp. 256-259. One approach in this general direction has been reported by Freedman and Shukla (1991), wherein references to other related work are given.

An alternative class of biologically and physiologically based models are those that strive to represent the behavior of some distinguished organ, particularly when the latter is subject to toxic insult. A well-studied class concerns the *liver;* a good overview of the "distributed parallel tube" liver model (and its predecessors and competitors) is given by Robinson (1992). Such models view the liver as a collection of enzyme-lined tubes through which blood flows carrying a substrate to be removed by enzyme action. Natural functional heterogeneities in the liver require formal mathematical recognition: this can be accomplished by the addition of one model parameter in a partially randomized setup.

6. RISK ASSESSMENT

An important application for the models discussed here is to quantitative *risk assessment*. The general objective of risk assessment is to estimate the type and incidence of detrimental biological effects associated with the introduction of various levels of pollutants into the environment. Of major but not exclusive concern are the biological effects upon human beings; the term pollutants refers not only to chemical and biological substances but also to ionizing and electromagnetic radiation and other physical agents, and to any combinations thereof. The term "biological effects" has often referred to cancer, but should also include genetic and developmental defects and other detrimental outcomes including psychological and behavioral abnormalities. Of course all such outcomes can in principle occur, in various combinations and severities, depending upon the exposure, and the nature and current status of the recipient of that exposure.

The *risk* attributable to a particular agent or substance can be thought of as a combination of the *hazard* or detrimental effect, *i.e.* toxicity, of that agent, *given* a level of exposure, and the extent and pattern of *exposure* to the agent. The task of risk assessment is to identify agents whose toxicity is a health threat to specified subpopulations, given exposure or dosage at specified levels, and to estimate the likely extent of exposure (dosage) of those subpopulations. Quantitative risk assessment then often presents its conclusions in simple numerical form. The stark form of the numerical statements typically quoted in the news media provokes concern by the general public, and skepticism by scientists who are aware of the various inferential difficulties encountered in obtaining those numbers; see *Wall Street Journal*,

August 6, 1992, and also Freedman and Zeisel (1988). Nevertheless, attempts to quantify suitably defined risks will be intensively sought in a Continuing attempt to rationalize and communicate, and in particular to assess the effects of both modifying pollutant introduction into the environment, and of environmental remediation. Problems of cost-effective risk reduction and of wise resource allocation are of great interest and concern; see *The Economist* (1992), and Keunreuther (1991) for more on the economics of waste and pollution management, and the cost-effectiveness of regulations as opposed to taxes on polluting technologies.

Efforts to improve the quality and credibility of risk assessment results have taken several forms. One is to clearly express the current state of scientific knowledge concerning cancer initiation mechanisms; see Hart *et al.* (1986) for example. The Hart committee's summary is in the form of 31 principles that address mechanisms of carcinogenesis, tests of cancer induction, epidemiology, exposure assessment, and risk assessment. The general multi-stage nature of the cancer development process has been recognized as the first principle derived from the mechanisms of carcinogenesis in the above review, and has been incorporated into the biologically-based pharmacodynamic models described in Section 5.

Assessment of human response to low doses of possibly toxic agents, alone or in combination, is an important regulatory issue. Realistic estimates of exposures to hazardous agents experienced by human beings in real-world conditions are often comparatively low, if protracted. Furthermore, exposure to chemical toxicants in addition to normal background exposures may well be at a comparatively low level. However, available experimental results with

laboratory animals are typically at a relatively high dose level, *i.e.* near to a maximum tolerable dose for the species or somewhat below. The problem of extrapolation from such laboratory results to the low values of risk-assessment interest poses difficult questions that have not been totally satisfactorily addressed in many cases.

For example, interest has focused on the possible existence of a *threshold* dose, a concentration below which a particular toxic agent would have zero response. The position of the Hart committee is expressed in its principle 3: "At the present state of knowledge, mechanistic considerations such as DNA repair and other biological responses, in general, do not prove the existence of, the absence of, or the location of a threshold for carcinogenesis."

Low-dose threshold phenomena must be experimentally investigated by actually submitting sets of experimental animals to a sequence of lower and lower doses, observing the numbers that respond, and interpreting the dose-response trend. Recent experimental work investigates the dose-response relationship of N-nitrosodiethylamine (NDEA) and N-nitrosodimethylamine (NDMA) and the development of esophageal and liver cancer, and other types as well. In this study, Peto *et al.* (1991a, 1991b), a large number, 4080, of Colworth/Wistar rats were given varying, but in particular low, drinking-water doses of the above agents, and the incidence of neoplasms, *e.g.* in the liver, was noted. Conclusion: at low doses the fraction of animals exhibiting lifetime neoplasms was nearly proportional to dose, "with no indication of any 'threshold'."

In another very recent study, Portier *et al.* (1992) investigated the response to dioxin, 2,3,7,8-TCDD, administered regularly (biweekly) after DEN initiation, of female Sprague-Dawley rats. The response was taken to be concentration of a dioxin-mediated protein in the liver. This concentration was predicted using two biologically-plausible mathematical models, an "additive" and an "independent" version. The additive model was interpreted to fit study data better than the "independent" model, but both fit adequately, and in neither case was there strong evidence of a threshold or strongly sigmoidal non-linear response. From a policy viewpoint this finding is interpreted to mean that safe exposure levels are lower than would be the case if a threshold were demonstrable.

The Portier *et al.* (1992) study assesses the *uncertainty* associated with its inferences by use of the re-sampling or "bootstrapping" methodology referred to earlier; see Efron and Tibshirani (1986). In Peto *et al.* (1991b) a formal two-parameter Weibull model is fitted but no uncertainty statements seem to be made about parameter estimates or extrapolated low-dose responses; perhaps this omission merely reflects the authors' skepticism concerning the parametric models' validity at truly low doses.

Conventional statistical attention to random sampling uncertainty, *e.g.* as addressed by bootstrapping, largely ignores the effect of model uncertainty. However, concern with interest and attention to this feature of much quantitative risk assessment is naturally evident. Note that an ultimate objective often is to provide credible and defensible cross-species "mouse to man" extrapolations of the effect of suspected toxins or carcinogens. It seems to be generally agreed that it is reasonable to regard "chemicals for which

there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans," see Hart *et al.* (1986), principle 8. However, this statement is vague and there are difficulties with its quantitative and qualitative interpretation; see Freedman and Zeisel (1988) and accompanying (discordant) discussion. See also Crouch and Wilson (1979), and Crouch, Wilson, and Zeise (1987) who have tried to show a statistical association between mouse and rat response; the reality of that association has been questioned by D. Freedman (Stanford statistics colloquium, 1992). More recently Talcott (1992) has pointed out the many places in an environmental risk assessment that are vulnerable to uncertainties, and recommends systematic attention to these so as to limit the use of arbitrary conservative assumptions and safety factors.

In summary, quantitative risk analysis based on models used for extrapolation of animal experiment dose responses to other species, notably humans, is demonstrably still somewhat inexact. The recognition of this fact has stimulated further research on the fundamental biological phenomena, and consequently more attention to development of mathematical models faithful to that of phenomena. Such work demands, and stimulates, fruitful interplay between representatives of different scientific disciplines. Issues of international, national, and local economics stimulate the acquisition of sound information on the risks potentially associated with exposures to substances produced by our technologies, so that cost-effective choices can be knowledgeably made.

7. EPIDEMIOLOGIC CASE STUDIES

In this concluding section we review approaches taken to assessing potential human risk from contaminated water in two different areas of the United States: Woburn, Massachusetts, and Battle Creek, Michigan. The discussion points up the difficulties of such epidemiological studies. Uncertainties include imperfect knowledge concerning exposure, and dose-response relationships when doses are chronic and to several toxic compounds when also many routes of entry and responses are possible. Nevertheless, serious attempts at quantitative assessments are valuable in that they focus energy on specific issues and questions, and on the revealed deficiencies in data and theory that are candidates for improvement. Recognition of sources of uncertainty in assessments also contributes to better understanding of the value of these assessments, and stimulates efforts to reduce and quantify uncertainties.

Case 1: The Woburn Well Water Case (Lagakos, *et al.*, 1986)

We summarize and discuss the model-based statistical analysis of a water-associated ecotoxicity situation; Lagakos, *et al.* (1986). To summarize: in 1979 it was discovered that two out of eight water wells servicing Woburn, Massachusetts, were contaminated with various organics: trichloroethylene, tetrachloroethylene, chloroform, tricholorotrifluoroethane, and dichloro-ethylene. Groundwater tests under eastern Woburn, where the two implicated wells (designated *G* and *H*) were located, revealed EPA-priority pollutants. The wells were closed in 1979. Subsequent studies by the Massachusetts Department of Public Health revealed a cancer mortality rate for Woburn that was significantly higher than that for the state and the six adjacent communities.

Woburn's childhood leukemia rate appeared to be elevated for the 1969-1979 period: 12 cases were diagnosed when 5.3 were expected (p-value = 0.008).

Lagakos *et al.* obtained data and performed statistical analyses to assess possible association between access to water from wells *G* and *H* and incidence rate of childhood leukemia. They also attempted to relate such water consumption to adverse pregnancy outcomes and childhood disorders; their logic was that the latter health effects are of shorter latency than leukemia and thus may be more sensitive indicators than is leukemia incidence.

The data that were analyzed statistically consisted first of 20 cases of childhood leukemia diagnosed in Woburn over roughly the *G* and *H* pumps' active period (1964-1983). Exposure to *G* and *H* water was scored by year and cumulatively, according to the residence history. A telephone sample survey was conducted in 1982 in order to obtain information on incidence of APO/CD during the period 1960-1982, along with mother's residence history. Care was taken in the survey, but since it managed to contact something like 50% of Woburn residents with listed phones, and since the many types of adverse responses were grouped into categories, the use of the survey data was criticized by some discussants of the paper.

Statistical analysis of the 20 leukemia cases was conducted with the aid of a statistical model, the so-called *Cox failure time regression model;* Cox 1972. That model relates the age-dependent rate of early occurrence of leukemia to exposure. Strength of association is measured by the degree of positivity of a regression parameter, which turned out to be positive with moderate statistical significance. A logistic regression approach when applied

to data on pregnancy outcomes and childhood disorders also indicated an association of some of these responses and access to *G, H* water.

Lagakos *et al.* carefully attempted to check for survey biases, such as could be caused by overreporting among those exposed to *G, H,* and underreporting among those unexposed; they concluded that these biases were negligible. (Note: this effort did not satisfy at least one discussant of the paper.) The effect of inexact exposure estimation was also assessed by redoing calculations based on a coarser partitioning of *G, H* exposure levels than that first used. Such a step resembles classical errors-in-variables strategies, *e.g.* the Wald grouping method, *cf.* Fuller (1987). The procedure resulted in the same significant associations as previously detected.

In summary, inference concerning risk of leukemia and CD/APO was conducted using data on exposure to Woburn wells *G* and *H* and mathematical models deemed appropriate for such investigation. The investigations concluded that their analysis, while showing positive association, did not explain the entirety of Woburn's leukemia excess. Little evidence was found of increase in spontaneous abortion or low birth weight, with increased *G, H* exposure, but perinatal/stillbirth rate was up, as were (strongly) eye/ear and chromosomal/oral cleft anomalies. Other positive associations were found as well.

Six discussants commented upon the reported study. All were free in pointing out deficiencies, many of which were acknowledged by the authors. Prominent among the deficiencies noted were (apparently unavoidable) difficulties with exposure assessment and the survey data, and the possibility of overinterpretation of positive indications of association because of the

"multiple testing" phenomenon; also, some doubt was cast on the accuracy of approximations used to calculate *p*-values, and to the sensitivity of the latter values to deletion/addition of single observations. All such valid comments contribute to a better understanding of the difficulties of conducting convincing studies of environmental risk; their recognition presumably will lead to improvements in future studies.

Case 2: Battle Creek Health Study (Freni and Bloomer, 1988)

In 1981 an aquifer servicing the Battle Creek, Michigan, area was found to be contaminated with various volatile organic chemicals (VOCs). The wells were subsequently closed. Groundwater contamination with the same VOCs was later detected in Dowagiac and in Springfield, adjacent to Battle Creek. The Michigan Department of Public Health proceeded to conduct a comprehensive epidemiologic study of the potential health effect of the contaminated drinking water; see Freni and Bloomer (1988); this is called the Battle Creek Health Study.

An initial literature review indicated that adverse effects of chronic exposure to particular VOCs had been observed only at levels much higher than those discovered in the Battle Creek drinking water. However, this information did not extend to situations involving multiroute exposure to multiple VOCs. Consequently, a *retrospective cohort study* was designed: a cohort of exposed people was compared to a reference or control cohort of unexposed people with respect to incidence of diseases or other health parameters during a follow-up period. The reference cohort was from neighborhoods comparable to the contaminated areas with respect to age, size, and value of dwellings; the individuals selected for both cohorts were comparable with respect to age and

sex. There were some refusals to participate (about 20% in exposed, and 30% in reference, cohorts), a common occurrence in such studies that is potentially biasing.

The quality of raw data on extent of exposure of the exposed cohort was "extremely poor", according to Freni and Bloomer (1988). It was necessary to construct a mathematical model to infer from the results of available well-monitoring data the time of start of residential well contamination and the total accumulated exposure (TAEVOC) of individuals; these latter estimates were supplemented by interview data, and when possible converted to inferred dosage in drinking water (TAEDOSE); estimated dosages varied considerably across individuals. As was true in the Woburn Study, dosage levels were indirect, and hence uncertain, although the Battle Creek Study devoted much thought and energy to quantifying individual exposure by drinking water but also from showering and bathing.

Health data were obtained from several sources: *interviews,* in which subjects were asked to recall diseases experienced in the past, and their date of diagnosis; *medical records; clinical examination* for subjects at least five years old; *mortality* and *hospital discharge rates.* Efforts to obtain a variety of possibly informative data seemed greater than those made in the Woburn Study.

It was judged likely that an interview bias existed: those in exposed areas, who became aware of possible exposure through the media, by word of mouth, or when interviewed, may recall more disease than others. However, analysis of the uncorrected 1976-1980 mortality data for Battle Creek is reported to have shown that the city had "significantly higher" rates for

eight of the state's ten leading causes of death; these include heart disease and cancer. The magnitudes of the effects are not reported.

Statistical models were brought into play to analyze the above data. The simplest and most traditional of these is the *odds ratio*, defined in terms of these numbers: for specified risk factor, R, and specified disease (or indicator thereof), D, denote

n_{DR} = Number exposed to risk factor R that exhibit disease D;

$n_{\bar{D}R}$ = Number exposed to risk factor R that do not exhibit disease D;

$n_{D\bar{R}}$ = Number <u>not</u> exposed to risk factor R that exhibit disease D;

$n_{\bar{D}\bar{R}}$ = Number <u>not</u> exposed to risk factor R that do not exhibit disease D.

Then the odds ratio (for D, given R) is computed as

$$\mathrm{OR}(D; R) = \frac{\text{Odds for } D, \text{ given } R}{\text{Odds for } D, \text{ given not-}R} = \frac{(n_{DR}/n_{\bar{D}R})}{(n_{D\bar{R}}/n_{\bar{D}\bar{R}})}$$

For example: Suppose 250 individuals (= study participants) consumed water with high VOC concentration (risk factor R); of these 50 = n_{DR} exhibited liver disease. A reference or control group of 500 individuals consumed water with low or normal VOC concentration; of these 10 = $n_{D\bar{R}}$ exhibited liver disease. Then the odds ratio for liver disease, D, given the high-VOC risk factor, R, is

$$\mathrm{OR} = \frac{50/200}{10/490} = 12.3,$$

an attention-getting number that strongly suggests an association of liver disease, D, with high-VOC risk factor, R. (No such levels were found in the Battle Creek Study.) A numerical value close to unity indicates neutrality so far as effect of the risk factor goes. A numerical factor less than unity suggests that absence of the specified risk factor is associated with greater

disease prevalence in the sample analyzed. This effect nay be caused by the action of an unsuspected additional risk factor in the reference group. The odds ratio statistic is very frequently employed in the Battle Creek Study, often adjusted for estimated exposure or dosage by stratification. In such cases the numbers in the various categories are small, so the sampling variability is large. As a result, only a few of the calculated odds ratios reach statistical significance at the (modest) level $p = 0.10$.

Another frequently-utilized statistical measure of effect was the *rate* ratio or relative risk; in words,

$$\mathrm{RR}(D; R) = \frac{\text{Number exhibiting } D \text{ per person-month exposed to } R}{\text{Number exhibiting } D \text{ per person-month of not-}R}$$

This index controls broadly for exposure.

Statistical modeling of realistically individually variable exposure or dosage responses were conducted by *multivariable regression analysis,* particularly the *proportional hazard* or *Cox model,* see Cox (1972), and the *logistic regression model,* Cox and Oakes (1984). These models were also utilized in the Woburn Study; both nay now be fitted to data using standard package computer programs, as may a variety of other relevant *generalized linear models;* see McCullagh and Nelder (1983); the latter techniques were available in 1986, and their application to the Battle Creek data could be of interest.

The statistical procedures carried out on the data involved the above models when viewed as appropriate, plus others. The simple general conclusion was that no positive or significant (below the $p = 0.1$ level) relationship between exposure to VOCs and adverse effects on health. In fact, a weak

reverse effect was noted: the data suggest an excess of abnormal response values in the reference or control cohort. This effect has not been explained.

Discussion

Despite careful attempts to control the relevance and quality of the data used, the associated health effects with contamination levels in both Woburn and Battle Creek appeared small. Furthermore, they often did not reach conventional levels of statistical significance.

Such outcomes may well have several explanations. One is that, despite considerable care, the data obtainable retrospectively on individual dosages and responses were simply inadequate to allow the detection of rather weak and individual-specific effects. Small effects are difficult to detect when exposed populations are homogeneous, but the samples studied may not have been homogeneous enough in response to the "contaminant treatment" level under investigation, to reveal the latter's influence over and above that of the prevailing background. Furthermore, the more sophisticated regression models used do not take account of the fact that data on dosage and health-effect responses are surrogate, in that they represent the variation of causal variables indirectly, in broad error-afflicted summary, and they are not designed to reflect the variation of individual responses to contaminants and background.

To make further progress in quantitative epidemiologic studies it appears necessary to obtain increasingly pertinent and inclusive dose and response data, where guidance for what data are needed will derive from improved understanding of biological response to chemical intruders. That same

understanding will permit the construction of models that can better be relied upon to predict health effects in a trustworthy manner.

8. SUMMARY AND CONCLUSIONS

This chapter furnishes an overview of a selection of the many mathematical models used in representing the flow, transformation, and fate of toxic substances in the environment, and eventually within organisms such as the human body. The presentation is in no way encyclopedic; for example, there is no discussion of air pollution generation, transport, and human exposure, a significant omission. References are provided to repositories of models of transport and exposure. The functionality of dose-response models, particularly for cancer, is described in some literary detail, without mathematical elaboration; references will allow interested readers access to details. Such mechanistic models are not now widely available at a fundamental level for many other health effects, a deficiency which appears to offer multifold research opportunities.

The users of models must face the task of *linking* or *integration* of *models* of various stages, from pollution generation, through transport, dispersion, and transformation, to eventual exposure and dosage of an organism to produce various health effects. The literature on methodology for this important linkage problem, with its attendant uncertainties, appears to be minuscule; see, however, Smith in Chapter 5 of Bloom and Poskitt (1988) who examine DNA adduct formation caused by ethylene oxide. This work emphasizes mechanistic differential equation tools at the expense of attempts to characterize inter-individual, and other, variability by stochastic models. It provides a start on the road towards credible interspecies extrapolation.

Through the consideration of two case studies concerning health effects or risks associated with contaminated drinking water, we appreciate the difficulty of establishing a causal link between presence of an elevated contaminant level and strong evidence of corresponding health effects. The credible reconstruction of historical exposure from available data is seen to be essential, but difficult and fraught with often unquantified uncertainty. Additionally, the variable susceptibility of those exposed can only add to the difficulty of linkage. This area appears to be a prime candidate for future research. For example, data on the response to toxic chemical agents in drinking water of individuals who are suffering from various forms of disease might well reveal magnified health effects. To learn this, the appropriate data must be available, and be analyzed. Eventually, after the physical transport and biological mechanisms are well enough understood, the impact of multiple results may be usefully anticipated and appropriate steps taken. More research appears necessary before this is reliably possible.

In various branches of science and technology it has been found useful to consider together, and possibly to judiciously combine, data on similar situations so as to achieve stronger quantitative estimates of effects; see Gaver *et al.* (1992). In medical and social science circles in the U.S. this activity is frequently called *meta analysis;* the term *overviews* is preferred by the prominent British biostatistician R. Peto. It appears likely that the techniques of this field, notably but not exclusively hierarchical Bayesian analysis, will find a place in the toolkits of those who analyze environmental transport and fate, exposure, and dose-response relations and data. The basic notion is that at least certain classes of situations, such as certain

Superfund sites eligible for cleanup, may have features in common that can be invoked to strengthen individual assessments of cleanup status assessment, for example. This would involve suitably combining (*not* uncritical pooling) of data from several similar sites with that of a specific site of interest so as to improve the estimate of its condition after a particular effort has been made. Likewise, assessments of health effects of certain pollutants that have been conducted at different times or places might be profitably brought together in an overall analysis. Such actions have precedent, but do not now appear to be commonly employed. For a status report on meta analysis in various fields, see Gaver, *et al.* (1992).

As was stated initially, those who make quantitative studies of environmental risk are essentially never able to conduct planned or designed experiments on human subjects. Consequently they are confronted with *observational data* that potentially contain biasing and confounding factors. A good account of effective statistical analyses of such difficult data is given by Cochran (1983) (edited and completed by L. Moses and F. Mosteller). This material should not be ignored by those health-effects analysts attempting to draw conclusions from environmental and observed response data. In particular, the careful use of modern nonlinear regression techniques in company with appropriately biologically motivated mechanistic models is to be encouraged in order to adjust for measured covariates such as age, gender, weight, or others while also properly modeling the biological phenomena. Recent work by Piegorsch and Casella (1992) is in this direction; they consider mouse genotoxicity data in the context of a hierarchical logistic or binomial model. See also the references in Sections 4, 5, and 6 above.

The aim of this chapter has been to describe some of the ways in which quantitative modeling and analytical techniques have been applied in the environmental areas of concern in this book. It is hoped that the result will be stimulating and helpful, especially to those new to this approach.

Acknowledgments

The following individuals assisted me in obtaining background for the above presentation. C. Travis, D. Hoel, S. Freni, S. Lagakos, B. Johnson, H. Gardner, S. Beal, P. J. Robinson, H. L. Carpenter, and the other members of the Conte Institute Monograph Writing Group. (The selection of information to present and its organization, accuracy, and emphasis are my responsibility alone.)

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Canberra, A.C.T. 2606
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Graduate School of Public Health
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1700 Main St.
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Statistics Department
University of California
Davis, CA 95616

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Dept. of Statistics
Southern Methodist University
Dallas, TX 75222

35. Prof. H. Solomon 1
Department of Statistics
Sequoia Hall
Stanford University
Stanford, CA 94305

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Woods Hole Oceanographic Institute
Woods Hole, MA 02543

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University of Washington
Seattle, WA 98195

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Cambridge, MA 02139